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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/810,262	03/26/2004	Stuart Naylor	674523-2029.1	1123

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EXAMINER	
CHEN, SHIN LIN	

ART UNIT	PAPER NUMBER
1632	

MAIL DATE	DELIVERY MODE
03/17/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/810,262	NAYLOR ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,12-14,16-18,47,48 and 50-57* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,12-14,16-18,47,48 and 50-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1-25-08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1-25-08 has been entered.

Applicants' amendments filed 4-23-07 and 1-25-08 have been entered. Claims 1, 50 and 51 have been amended. Claims 15 and 49 have been canceled. Claims 55-57 have been added. Claims 1-6, 12-14, 16-18, 47, 48 and 50-57 are pending and under consideration.

Information Disclosure Statement

2. The information disclosure statement (IDS) submitted on 1-25-08 was filed on the filing date of the request for continued examination on 1-25-08. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Priority

The parent applications 09/787,562, PCT/GB99/03181, PCTGB98/02885, United Kingdom 9901906.9 and 9903538.8 fail to disclose the subject matter of the instant invention, i.e. a method for inhibiting oculate neovascularization by delivering to the target cells in the eye of a subject a vector expressing an angiostatic gene product under the control of a promoter.

Therefore, the priority dates of those parent applications are not granted. Thus, the priority of the instant invention is the filing date of the present application, 3-26-04.

Claim Objections

3. Claim 1 is objected to because of the following informalities: It appears that VEGFR1 and FLT-1 are synonyms. Deleting one of the terms would be remedial. Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-6, 12-14, 16-18, 47, 48 and 50-57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "FLT-1" in claim 1 is vague and renders the claim indefinite. The term "FLT-1" is an abbreviation that can stand for various meanings. It is unclear what meaning is intended in the claim. Claims 2-6, 12-14, 16-18, 47, 48 and 50-57 depend from claim 1 but fail to clarify the indefiniteness.

The term "CMV" in claim 5 is vague and renders the claim indefinite. The term "CMV" is an abbreviation that can stand for various meanings. It is unclear what meaning is intended in the claim.

The term "VMD2" in claims 55-57 is vague and renders the claim indefinite. The term "VMD2" is an abbreviation that can stand for various meanings. It is unclear what meaning is intended in the claim.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-6, 12-14, 16, 17, 47, 48, 53, 55 and 56 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibiting retinal neovascularization by direct injection to target cells in the eye an expression vector expressing soluble truncated form of the VEGF receptor Flt-1 (or sFlt-1), which lacks the membrane-proximal immunoglobulin-like domain, the transmembrane spanning region and the intracellular tyrosine-kinase domain generated by alternative splicing, does not reasonably provide enablement for inhibiting retinal or choroidal neovascularization in the eye of a subject by direct injection of an expression vector expressing VEGF receptor 1 or FLT-1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considered whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a

specification meets the enablement requirement, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d at 737, 8 USPQ2d 1400, 1404 (Fed. Cir.1988)).

Furthermore, the USPTO does not have laboratory facilities to test if an invention with function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raises and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The claims are directed to a method for inhibiting retinal or choroidal neovascularization in the eye of a subject comprising delivering via direct injection to target cells in the eye an equine infectious anemia virus (EIAV)-based lentiviral vector comprising a promoter, such as a physiologically regulated promoter (e.g. hypoxic response element) or a constitutive promoter (e.g. CVM promoter) operably linked to a polynucleotide sequence encoding an endostatin, angiostatin, vascular endothelial growth factor receptor 1 (VEGFR1), FLT-1, or PEDF. Claim 6 specifies the retinal or choroidal neovascularization results in proliferative diabetic retinopathy (PDR) or age-related macular degeneration (AMD) in the subject. Claim 7 specifies the ocular neovascularization is choroidal or retinal neovascularization. Claims 12 and 13 specify the target cells are retinal cells, such as retinal pigment epithelial cells. Claim 14 specifies the delivery is via direct sub-retinal injection. Claims 16-18 specify the vector further comprises a

polynucleotide sequence encoding at least one additional angiostatic gene product. Claims 47 and 48 specify the promoter further comprises an enhancer sequence, and the promoter and enhancer direct expression in RPE cells or photoreceptor cells. Claims 50-52 specify the angiogenic gene product endostatin and/or angiostatin is codon optimized. Claims 53 and 54 specify the promoter sequence is RPE-specific promoter sequence. Claims 55-57 specify the promoter sequence is VMD2 promoter sequence.

The specification discloses preparation of EIAV-OBHRE recombinant LentiVector and shows hypoxially regulated LacZ expression in transduced human retinal pigment epithelial cells in vitro, (example 2), and subretinal injection of LentiVector shows OBHRE mediated LacZ expression in localized regions of the laser treated retina (example 3). The claims encompass inhibiting retinal or choroidal neovascularization in the eye of a subject by direct injection to target cells in the eye an EIAV-based lentiviral vector comprising a polynucleotide encoding a VEGFR1 or FLT-1 under the control of a promoter. The specification fails to provide adequate guidance and evidence for how to inhibit retinal or choroidal neovascularization in the eye of a subject by direct injection to target cells in the eye an EIAV-based lentiviral vector comprising a polynucleotide encoding a VEGFR1 or FLT-1 under the control of any promoter.

The state of the art demonstrates that soluble truncated form of the VEGF receptor Flt-1 (or sFlt-1), which lacks the membrane-proximal immunoglobulin-like domain, the transmembrane spanning region and the intracellular tyrosine-kinase domain, works as antagonist of VEGF and can inhibit retinal neovascularization. Bainbridge et al., 2002 (Gene Therapy, Vol. 9, p. 320-326) reports that overexpression of VEGF in photoreceptor cells causes retinal neovascularization in transgenic mice and sFLt-1, which lacks the membrane-proximal

immunoglobulin-like domain, the transmembrane spanning region and the intracellular tyrosine-kinase domain, inhibits angiogenesis and it is an inhibitor of VEGF (e.g. p. 320, right column to 1st paragraph of p. 321). There is no evidence of record that shows full-length VEGFR1 or FLT-1 would be able to inhibit retinal or choroidal neovascularization. Absent specific guidance and evidence, one skilled in the art at the time of the invention would not know how to inhibit retinal or choridal neovascularization by using an EIAV-based vector expressing a VEGFR1 or FLT-1, and would require undue experimentation to practice over the full scope of the invention claimed. This is particularly true based upon the nature of the claimed invention, the state of the art, the unpredictability found in the art, the teaching and working examples provided, the level of skill which is high, the amount of experimentation required, and the breadth of the claims.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 1-6, 12-14, 16-18, 47, 48 and 53-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stout et al., 2002 (WO 02/49677 A1, IDS-AL).

The claims are directed to a method for inhibiting retinal or choroidal neovascularization in the eye of a subject comprising delivering via direct injection to target cells in the eye an equine infectious anemia virus (EIAV)-based lentiviral vector comprising a promoter, such as a physiologically regulated promoter (e.g. hypoxic response element) or a constitutive promoter (e.g. CVM promoter) operably linked to a polynucleotide sequence encoding an endostatin, angiostatin, vascular endothelial growth factor receptor 1 (VEGFR1), FLT-1, or PEDF. Claim 6 specifies the retinal or choroidal neovascularization results in proliferative diabetic retinopathy (PDR) or age-related macular degeneration (AMD) in the subject. Claims 12 and 13 specify the target cells are retinal cells, such as retinal pigment epithelial cells. Claim 14 specifies the delivery is via direct sub-retinal injection. Claims 16-18 specify the vector further comprises a polynucleotide sequence encoding at least one additional angiostatic gene product. Claims 47 and 48 specify the promoter further comprises an enhancer sequence, and the promoter and enhancer direct expression in RPE cells or photoreceptor cells. Claims 53 and 54 specify the promoter sequence is RPE-specific promoter sequence. Claims 55-57 specify the promoter sequence is VMD2 promoter sequence.

Stout teaches that lentiviruses are known to infect and transducer a wide variety of terminally differentiated, mitotically active or inactive human cell types, such as human retinal, corneal, retinal pigment epithelial and vascular endothelial cells, and the transduction efficiency

is very high (e.g. p. 14, lines 15-22). Stout teaches a method of inhibiting intraocular neovascularization in an individual having an ocular disease, such as proliferative diabetic retinopathy (PDR) and age-related macular degeneration (AMD), by administering to said individual a lentiviral vector comprising a therapeutic gene that inhibits intraocular neovascularization, wherein said therapeutic gene includes endostatin, angiostatin, a fusion protein of endostatin and angiostatin, and soluble FLT-1 (fms-like tyrosine kinase 1 receptor) (e.g. 49-50, claims 5-8). The lentiviral vector can contain strong promoters such as CMV or HTLV promoters, or other promoters known to be active in human retinal, corneal or retinal pigment epithelial cells (e.g. p. 15, lines 14-18).

Stout does not specifically teach using EIAV-based vector, enhancer sequence, or VMD2 promoter sequence.

It would have been obvious for one of ordinary skill in the art at the time of the invention to use EIAV-based vector for the claimed method because EIAV is a type of lentivirus and Stout teaches using lentiviruses expressing angiostatic protein to inhibit intraocular neovascularization. It also would have been obvious for one of ordinary skill in the art at the time of the invention to use VMD2 promoter sequence because Stout teaches using promoter known to be active in retinal pigment epithelial (RPE) cells and VMD2 is a PRE-specific promoter. Since adding enhancer sequence to aid promoter in stimulating gene expression was well known in the art, it would be obvious for one of ordinary skill in the art to use enhancer sequence.

One having ordinary skill in the art at the time the invention was made would have been motivated to do so in order to inhibit intraocular neovascularization as taught by Stout with reasonable expectation of success.

11. Claims 1, 2, 6, 12, 14 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Igarashi et al., 2003 (Gene Therapy, Vol. 10, p. 219-226).

The claims are directed to a method for inhibiting retinal or choroidal neovascularization in the eye of a subject comprising delivering via direct injection to target cells in the eye an equine infectious anemia virus (EIAV)-based lentiviral vector comprising a promoter, such as a physiologically regulated promoter or a constitutive promoter (e.g. CVM promoter) operably linked to a polynucleotide sequence encoding an endostatin, angiostatin, vascular endothelial growth factor receptor 1 (VEGFR1), FLT-1, or PEDF. Claim 6 specifies the retinal or choroidal neovascularization results in proliferative diabetic retinopathy (PDR) or age-related macular degeneration (AMD) in the subject. Claim 12 specifies the target cells are retinal cells. Claim 14 specifies the delivery is via direct sub-retinal injection. Claim 47 specifies the promoter further comprises an enhancer sequence.

Igarashi teaches preparation of a HIV vector expressing mouse angiostatin protein under the control of CAG promoter (e.g. p. 224, left column), and the HIV-angiostatin was injected intravitreally into mouse eye (e.g. Figure 4). Igarashi shows that lentivirus-mediated expression of angiostatin efficiently inhibits neovascularization in a murine proliferative retinopathy model (see Title).

Igarashi does not specifically teach using EIAV-based vector or enhancer sequence.

It would have been obvious for one of ordinary skill in the art at the time of the invention to use EIAV-based vector for the claimed method because EIAV is a type of lentivirus and Igarashi teaches using HIV-angiostatin vector and shows lentivirus-mediated expression of

angiostatin efficiently inhibit retinal neovascularization. Since adding enhancer sequence to aid promoter in stimulating gene expression was well known in the art, it would be obvious for one of ordinary skill in the art to use enhancer sequence.

One having ordinary skill in the art at the time the invention was made would have been motivated to do so in order to efficiently inhibit neovascularization in a murine proliferative retinopathy model as taught by Igarashi with reasonable expectation of success.

12. Claims 1, 18 and 50-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stout et al., 2002 (WO 02/49677 A1, IDS-AL) in view of Narum et al., 2001 (Infection and Immunity, Vol. 69, No. 12, p. 7250-7253).

The claims are directed to a method for inhibiting retinal or choroidal neovascularization in the eye of a subject comprising delivering via direct injection to target cells in the eye an equine infectious anemia virus (EIAV)-based lentiviral vector comprising a promoter, such as a physiologically regulated promoter or a constitutive promoter (e.g. CVM promoter) operably linked to a polynucleotide sequence encoding an endostatin, angiostatin, vascular endothelial growth factor receptor 1 (VEGFR1), FLT-1, or PEDF. Claim 18 specifies the angiostatic gene product is endostatin and the EIAV-based vector further comprises a polynucleotide encoding angiostatin. Claims 50-52 specify the angiogenic gene product endostatin and/or angiostatin is codon optimized.

Stout teaches that lentiviruses are known to infect and transducer a wide variety of terminally differentiated, mitotically active or inactive human cell types, such as human retinal, corneal, retinal pigment epithelial and vascular endothelial cells, and the transduction efficiency

is very high (e.g. p. 14, lines 15-22). Stout teaches a method of inhibiting intraocular neovascularization in an individual having an ocular disease, such as proliferative diabetic retinopathy (PDR) and age-related macular degeneration (AMD), by administering to said individual a lentiviral vector comprising a therapeutic gene that inhibits intraocular neovascularization, wherein said therapeutic gene includes endostatin, angiostatin, a fusion protein of endostatin and angiostatin, and soluble FLT-1 (fms-like tyrosine kinase 1 receptor) (e.g. 49-50, claims 5-8). The lentiviral vector can contain strong promoters such as CMV or HTLV promoters, or other promoters known to be active in human retinal, corneal or retinal pigment epithelial cells (e.g. p. 15, lines 14-18).

Stout does not specifically teach using codon optimized polynucleotide encoding endostatin and/or angiostatin.

Narum teaches that optimizing codon usage in DNA vaccine can improve protein expression and consequently the immunogenicity of gene fragment in DNA vaccine for organisms whose codon usage differs substantially from that of mammals (e.g. abstract).

It would have been prima facie obvious for one of ordinary skill in the art at the time of the invention to use codon optimized DNA sequence of endostatin or angiostatin because Narum teaches codon optimization can improve protein expression.

One having ordinary skill in the art at the time the invention was made would have been motivated to do so in order to increase protein expression as taught by Narum with reasonable expectation of success.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Shin-Lin Chen, Ph.D.

/Shin-Lin Chen/
Primary Examiner, Art Unit 1632